American Journal of Medical Genetics 63:434–437 (1996)

Non-Mosaic Tetrasomy 9p in a Liveborn Infant With Multiple Congenital Anomalies: Case Report and Comparison With Trisomy 9p

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Tetrasomy of the short(p) arm of chromosome 9 has been reported in few cases. Most of these children present with microbrachycephaly, wide forehead, hypertelorism, low-set, malformed ears, beaked noses, and micrognathia. Additional anomalies include short neck, congenital heart disease, genital abnormalities, multiple limb defects, hypotonia, and early death. © 1996 Wiley-Liss, Inc.

KEY WORDS: chromosome 9, tetrasomy 9p, trisomy 9p, multiple congenital anomalies

INTRODUCTION

Tetrasomy of the short(p) arm of chromosome 9 has been reported in 16 cases to date [Balestrazzi et al., 1983; Cavalcanti et al., 1987; Garcia-Cruz et al., 1982; Ghymers et al., 1973; Jalal et al., 1991; Moedjono et al., 1980; Papenhausen et al., 1990; Peters et al., 1982; Schafer et al., 1991; Shapiro et al., 1985; Wisniewski et al., 1978]. Most children present with specific craniofacial abnormalities including microbrachycephaly with wide forehead, hypertelorism, low-set, malformed auricles, beaked nose with wide nasal root, and micrognathia. Short neck, congenital heart disease, genital abnormalities, arthrogryposis, talipes equinovarus, brachydactyly with nail hypoplasia, hypotonia, early death, and moderate to severe mental retardation in the survivors are also common. We present a new case of a female infant with tetrasomy 9p who well illustrates the phenotype and compare this case and previously reported cases with trisomy of chromosome 9p.

CLINICAL REPORT

The patient was first evaluated at age 5 days due to the presence of multiple congenital anomalies. She was born to a 20-year-old father and 22-year-old G2P1 mother after a 35-week pregnancy. Mother reported no exposure to teratogens but did have a bladder infection treated with antibiotics at 4 months gestation. Mother described decreased fetal movement. A prenatal ultrasound at 5 months was described as normal. Family history was non-contributory for children with birth defects or children or adults with mental retardation. The patient was born by spontaneous vaginal delivery after premature rupture of membranes. Apgar scores were 5, 6, and 8 at 1, 5, and 10 minutes, respectively. She received brief resuscitation by O_2, suctioning, and mask breathing. The placenta was described as normal appearing with a normal cord insertion but the umbilical cord was described as very short.

On physical examination length was 43 cm (15th centile), weight was 1,580 g (3rd centile), and OFC was 28 cm (50th centile for 30 weeks gestation). Craniofacial findings (Figs. 1, 2) included brachycephaly with severe occipital flattening, large posterior and anterior fontanels, open metopic suture, and a furrowed, posteriorly sloping brow. The ears were low set and posteriorly rotated with an overfolded helix. Telecanthus was present. The palpebral fissures were down slanting and narrow with microphthalmia (corneal dimensions of 8 mm bilaterally). There was a wide nasal bridge and root with a large nose with a beaked tip. Also present were malar hypoplasia, micrognathia, a short philtrum, thin upper lip, and downturned corners of the mouth. The tongue was held out of the mouth and there was a normal palate with prominent palatine ridges.

The neck was short with thick nuchal folds. The chest was small and narrow with no murmurs appreciated. The labia majora were large and the clitoris was hypoplastic. Clinocamptodactyly of the fifth finger, short bulbous thumbs, and generalized brachydactyly were present bilaterally. The elbows and shoulders were dislocatable and there were fixed contractures at both elbows. There was bilateral talipes equinovarus. The skin exhibited generalized lentigines, the nails were hypoplastic, and the anterior hairline was receding. Musculature demonstrated normal mass but decreased strength. Neurologically, she had decreased tone, a high-pitched cry, and poor habituation to stimulus.

Received for publication June 12, 1995; revision received January 22, 1996.

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Figs. 1 and 2. Proposita: 1) AP; Wide forehead with beaked nose, downslanting palpebral fissures, narrow palpebral fissures. 2) Lateral; low-set, posteriorly rotated, malformed ears, and micrognathia.

Echocardiogram demonstrated a large atrial septal defect and patent ductus arteriosus. Radiologically, there were 11 rib pairs with no other bony abnormalities noted. The positional abnormalities of the hands, feet, and elbows were reported with no joint dislocations. Cranial sector scan was not interpretable.

The child had a stormy course with recurrent episodes of sepsis. There never were any signs of development beyond a social smile. She never left the hospital and died at age 6 weeks. An autopsy was refused.

CYTOGENETICS

Chromosomes were prepared from peripheral blood lymphocytes from the proposita and her mother and were G-banded by the method of Seabright [1971]. Analysis of 106 metaphases from the proband demonstrated an abnormal female karyotype in all cells. This karyotype was characterized by the presence of a supernumerary chromosome which appeared, by banding pattern (maximum banding level of 550) to be an isochromosome of 9p (Fig. 3). Fluorescence in situ hy-

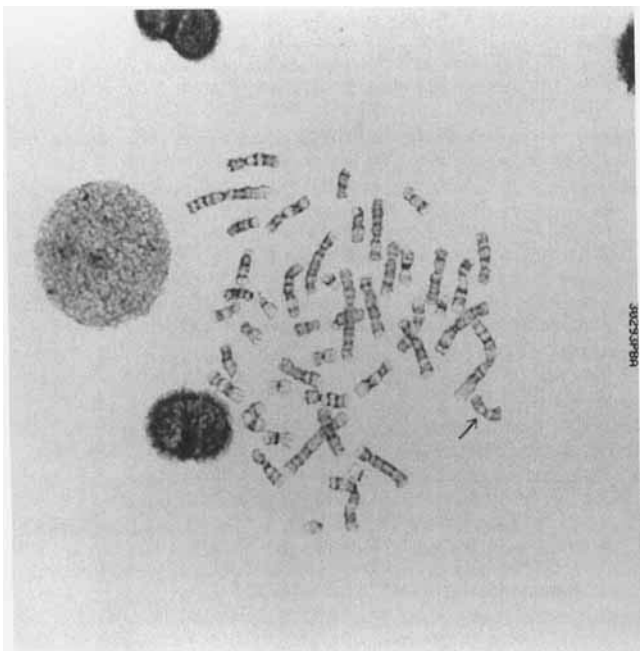

Fig. 3. G-banded metaphase spread from proposita. The arrow indicates the i(9p).

Fig. 4. Metaphase spread after hybridization with chromosome 9-specific painting probe. Both normal chromosomes 9 and the i(9p) hybridized with the probe.

TABLE I. Clinical Findings and Comparison of Trisomy and Tetrasomy 9p

Manifestation	Trisomy 9p[a] N = 44	Percentage	Tetrasomy 9p[b] N = 16	Percentage	Patient
Low birth weight	5/44	11	9/16	56	+
Short stature	37/44	84	11/16	69	−
Microcephaly	12/44	27	2/16	75	+
Brachycephaly	1/44	2	8/16	50	+
Wide forehead	2/44	5	9/16	56	+
Hypertelorism	35/44	80	12/16	75	−
Epicanthic folds	7/44	16	10/16	63	+
Downslant palpebral fissures	30/44	68	4/16	25	+
Microphthalmia	1/44	2	9/16	56	+
Low-set ears	4/44	9	12/16	75	+
Malformed ears	40/44	91	13/16	81	+
Beaked nose	32/44	72	14/16	88	+
Cleft lip/palate	4/44	9	9/16	56	−
Micrognathia	10/44	23	14/16	88	+
Short neck	7/44	16	12/16	75	+
Congenital heart disease	8/44	18	14/16	88	+
Genital abnormalities	2/44	5	13/16	81	+
Talipes equinovarus	1/44	2	9/16	56	+
Arthrogryposis	2/44	5	11/16	69	+
Nail hypoplasia	34/44	77	14/16	88	+
Brachydactyly	3/44	7	11/16	69	+
Camptodactyly	6/44	14	7/16	44	+
Developmental delay	41/44	93	3/16	18	?

[a] Centerwall et al., 1977; Cuoco et al., 1982; Orye et al., 1975; Shapiro et al., 1985.
[b] Calvieri et al., 1988; Cavalcanti et al., 1987; Jalal et al., 1991; Schafer et al., 1991.

bridization (FISH) with a chromosome 9-specific painting probe (Oncor, cat. number P5311-BIO) confirmed that both arms of the supernumerary chromosome originated from chromosome 9 (Fig. 4). Thus the proband's karyotype, based in both banding pattern and FISH, was most likely 47,XX,+i(9p). Analysis of 106 cells rules out 3% or greater mosaicism in the blood with 95% confidence [Hook, 1977]. Twenty metaphases from the mother and father were analyzed and these showed normal karyotypes.

DISCUSSION

While there is considerable phenotypic overlap between tetrasomy and trisomy 9p, tetrasomy 9p presents as a much more severe phenotype than trisomy 9p (Table I). Patients with tetrasomy 9p are more likely to have varying degrees of congenital heart disease, genital anomalies, joint contractures with many cases of frank dislocation, low birth weight, and early death. Short stature and mental retardation are less often seen in tetrasomy 9p due to the likelihood of early death. One author [Cavalcanti et al., 1987] feels that little consequence occurs because of the additional segment. It should be pointed out that the survival rate longer than one year of life of tetrasomy 9p is only 25%, whereas in the cases of trisomy 9p the survival rate is 75% for the same age grouping. Facial characteristics that are significantly different in tetrasomy 9p from trisomy 9p are brachycephaly, wide forehead, microphthalmia, low-set ears, cleft lip and palate, and micrognathia. It is certainly possible based on this report and comparisons with trisomy 9p cases that tetrasomy 9p may be a recognizable chromosomal syndrome.

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